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Expert panel recommendation

Expert recommendations for the diagnosis and treatment of iron-deficiency anemia during pregnancy and the postpartum period in the Asia-Pacific region

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Abstract

Anemia during pregnancy and the postpartum period is commonly caused by iron deficiency and is a significant worldwide issue with severe consequences for both mother and developing fetus. From a worldwide perspective, iron-deficiency anemia (IDA) during pregnancy is highest in the Asia-Pacific region; however, there has been little guidance in this region for safe and effective treatment. An expert panel was convened to develop a concise and informative set of recommendations for the treatment of IDA in pregnant and postpartum women in the Asia-Pacific region. This manuscript provides these recommendations and aims to reduce the morbidity and mortality associated with IDA in pregnant and postpartum women in the Asia-Pacific region. The consensus recommendations define anemia as a hemoglobin (Hb) level <10.5 g/dL during pregnancy and <10 g/dL during the postpartum period, and provide cut-off Hb levels to

initiate therapy with oral iron, intravenous iron or red blood cell transfusion.

Keywords: Anemia; iron deficiency; iron therapy; postpartum; pregnancy.

Introduction

Anemia is one of the most prevalent diseases worldwide, affecting 24.8% of the human population (1.62 billion people) (Table 1), and is a major health concern [3, 29]. Iron shortage is the single most common nutritional deficit in the world [3, 8] and is the major cause of anemia, accounting for approximately 50% of cases [28, 29]. The prevalence of iron-deficiency anemia (IDA) varies among countries but is a particular problem in the developing world, reflecting differences in race, socio-economic factors, nutritional habits, medical care and the frequency of parasitic illnesses [8]. Numerous countries conduct interventions to reduce anemia, particularly in susceptible groups, such as pregnant women and young children.

Anemia during pregnancy is a significant concern with the World Health Organization (WHO) estimating a prevalence of 41.8% amongst pregnant women (Table 1) [29]. Iron demand increases rapidly in the second and third trimester of pregnancy with the needs of the developing fetus, with a daily requirement of up to 10 mg [21]. Iron absorption from the diet also increases during pregnancy through upregulation of iron transporters in the gut [19]; however, this increase in absorption is not sufficient to meet the demand during the latter stages of pregnancy. Therefore, iron balance depends largely upon maternal iron stores [8, 9]. A pre-pregnancy store of more than 500 mg of iron is required to avoid iron deficiency during pregnancy, yet such adequate levels of iron are only present in 20% of menstruating women before pregnancy ensues [3]. These iron store deficits are exacerbated by the blood loss experienced during the delivery process and add to the considerable risk of developing postpartum anemia [9].

The consequences of IDA during pregnancy are often serious and long lasting for both the mother and fetus [8, 22] (Table 2). Expectant mothers with anemia often experience increased fatigue levels, reduced exercise performance and reduced mental performance [8, 22]. Furthermore, severe anemia [hemoglobin (Hb) <9 g/dL] is related to an increased risk of prematurity, small for gestational-age babies and spontaneous abortion [8]. Fetal iron metabolism is com-

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Table 1 Worldwide estimated prevalence of anemia [29].

Population group	Prevalence (%)
Pre-school-age children	47.4
School-age children	25.4
Pregnant women	41.8
Non-pregnant women	30.2
Men	12.7
Elderly	23.9
Total population	24.8

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Table 2 Consequences of IDA during pregnancy and postpartum [8, 9, 20, 22].

Mother	Fetus
<ul style="list-style-type: none"> • Fatigue • Increased risk for blood transfusion • Reduced physical performance • Reduced mental performance • Infection • Risk of hospitalization • Inhibited lactation • Postpartum depression: “baby blues” 	<ul style="list-style-type: none"> • Increased mortality • Reduced birth weight • Increased preterm birth • Growth retardation • Neurologic impairment • Impaired placental growth

IDA = iron-deficiency anemia.

pletely dependent upon maternal iron delivery via the placenta and so the effects of anemia on the fetus are directly related to the extent of maternal iron deficiency with increased mortality linked to severe IDA [8]. Considerable efforts to decrease the prevalence of IDA during pregnancy through preventative methods have been largely unsuccessful, and access to new therapies, such as intravenous (i.v.) iron and erythropoiesis-stimulating agents (ESAs), readily

available in the USA or Europe, can be limited in settings where resources are scarce and guidance is negligible.

Currently, there are three main options for the treatment of IDA: oral iron, i.v. iron and red blood cell transfusion. ESAs can also be used to treat anemia in some situations [7]. Recent recommendations, published in Europe and North America, include oral iron for the treatment of mild-to-moderate IDA during pregnancy with i.v. iron suggested for those unresponsive to oral treatment [20] (Table 3). The high costs associated with therapies, such as ESAs often prevent their use in some of the world's developing regions where anemia is most common.

Treatment of IDA arising during pregnancy and the postpartum period

Oral iron

Oral iron, administered in the form of ferrous sulphate, ferrous fumarate, ferrous gluconate or iron hydroxide polymaltose complex, is considered the current standard for the treatment of IDA and is most commonly prescribed in cases of mild-to-moderate anemia [8, 9]. The benefits of oral iron intervention include ease of use since no medical expertise is required for administration. However, limited efficacy and low patient compliance are often an issue, particularly due to gastrointestinal side effects [18, 20]. As such, oral iron may take a long time to correct IDA. Moreover, among the different oral iron preparations, ferrous salts, but not a polysaccharide-ferric iron complex lead to oxidative stress as evidenced by increased levels of non-transferrin bound iron (or NTBI) [14].

I.v. iron

The use of i.v. iron to treat IDA in pregnant women was first examined almost 60 years ago; enhanced Hb levels following

Table 3 European and North American guidelines for the treatment of IDA during pregnancy [5, 11, 20].

Swiss Society of Obstetrics and Gynaecology	The Network for Advancement of Transfusion Alternatives (NATA)
Pregnancy <ul style="list-style-type: none"> • Oral iron in patients with mild-to-moderate IDA (Hb 9–10.5 g/dL) • I.v. iron in second and third trimester in patients: <ul style="list-style-type: none"> – Unresponsive to oral iron – With severe IDA (Hb <9 g/dL) – With other factors such as requirement for rapid repletion (Jehovah's Witnesses etc) Postpartum <ul style="list-style-type: none"> • Oral iron in patients with mild anemia (Hb 9.5–12 g/dL) • I.v. iron in moderate-to-severe anemia (Hb 8.5–9.5 g/dL) <ul style="list-style-type: none"> – Consider ESAs if Hb <8 g/dL • Consider transfusion if Hb <6 g/dL 	<ul style="list-style-type: none"> • Oral iron in first and second trimester • Consider i.v. iron after 14 weeks' gestation in patients unresponsive to oral iron (Hb increase <0.5 g/dL in 2 weeks) • I.v. iron in third trimester in case of IDA • If available, test serum ferritin for iron stores <ul style="list-style-type: none"> • Without ongoing bleeding • I.v. iron if Hb 6–9.5 g/dL <ul style="list-style-type: none"> – ESA can be used in non-responders • Consider transfusion if Hb <6 g/dL • Early after delivery, ferritin is false normal Do not test before 6–12 weeks after birth

IDA = iron-deficiency anemia; i.v. = intravenous; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin.

Table 4 Estimated prevalence of anemia in pregnant women (1993–2005) [29].

WHO region	Prevalence of anemia in pregnant women (%) [95% CI]	Number of pregnant women affected (millions) [95% CI]
Africa	57.1 [52.8–61.3]	17.2 [15.9–18.5]
Americas	24.1 [17.3–30.8]	3.9 [2.8–5.0]
Southeast Asia	48.2 [43.9–52.5]	18.1 [16.4–19.7]
Europe	25.1 [18.6–31.6]	2.6 [2.0–3.3]
Eastern Mediterranean	44.2 [38.2–50.3]	7.1 [6.1–8.0]
Western Pacific	30.7 [28.8–32.7]	7.6 [7.1–8.1]
Global	41.8 [39.9–43.8]	56.4 [53.8–59.1]

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Table 5 Overview of treatment practice according to the panel members.

Country	Average patient age (years)	Prevalence of IDA	Country-specific guidelines?	Hb cut-offs for treatment (based on available guidelines or own practice experience)
Bangladesh	25	50% pregnancy 50% postpartum	Institute of Public Health and Nutrition (IPHN) 2002 (oral iron and blood transfusion)	First trimester • > 10 g/dL (oral iron) • < 10 g/dL (i.v. iron) Second and third trimester • < 9 g/dL (i.v. iron) • < 8 g/dL (blood transfusion)
China	28–30	6% pregnancy 7% postpartum	Yes (oral iron, i.v. iron and blood transfusions)	First trimester • > 10 g/dL (oral iron) Second and third trimester • < 9 g/dL (oral iron) • < 7 g/dL (i.v. iron) • < 8 g/dL before delivery (blood transfusion)
Indonesia	8–48	67% pregnancy 72% postpartum	Yes (oral iron, i.v. iron)	Second and third trimester • < 10 g/dL (i.v. iron) • < 7 g/dL (blood transfusion)
Pakistan	22–34	88% pregnancy Postpartum: no data	None	7–9 g/dL • 14–36 weeks (i.v. iron) • > 36 weeks (blood transfusion) 6–7 g/dL • Asymptomatic (i.v. iron) • Symptomatic (blood transfusion) < 6 g/dL • Blood transfusion
Philippines	35	44% pregnancy 43% postpartum	None	• > 8 g/dL oral iron • < 8 g/dL blood transfusion • Avoid blood transfusion if possible
Singapore	25–30	10–24% pregnancy Postpartum: no data	None	First to third trimester • 8–11 g/dL (oral iron/i.v. iron) • < 8 g/dL (blood transfusion)
Thailand	25–30	10–24% pregnancy Postpartum: no data	None	First and third trimester • 7–11 g/dL (oral iron) • < 7 g/dL (blood transfusion) Second trimester • 7–10.5 g/dL (oral iron) • < 7 g/dL (blood transfusion)
Vietnam	15–50	32% pregnancy Postpartum: no data	None	• ≥ 8 g/dL oral iron + folate • < 8 g/dL blood transfusion + folate

IDA = iron-deficiency anemia; Hb = hemoglobin; i.v. = intravenous.

Table 6 Overview of key treatment issues for the Asia-Pacific region.

Education	<ul style="list-style-type: none"> • In some areas, testing for anemia is not seen as a priority since severe anemia is not perceived as a major problem • Issues surrounding the prescription of oral iron and blood transfusions based on empirical rather than evidence-based experience • Patients avoid injections which means that physicians have less experience in giving them • Fear of iron-dextran anaphylaxis from previous trials • Physicians are unaware of the difference between i.v. iron dextran and i.v. iron sucrose • Lack of information on i.v. iron use • Lack of guidelines for the use of i.v. iron in pregnancy
Cause of anemia	<ul style="list-style-type: none"> • Factors other than iron deficiency can cause anemia • Thalassemia is prevalent in the Asia-Pacific region
Diet	<ul style="list-style-type: none"> • Low iron diet compared with Europe and North America • Socio-economic background can result in greater risk of iron deficiency
Transfusions	<ul style="list-style-type: none"> • Infection risk (HIV, hepatitis B and C) [7] [24] • Shortage of available blood • Cost
Cost of i.v. iron	<ul style="list-style-type: none"> • Governments may not finance treatment • Where governments do not fund treatments, patients cannot afford i.v. iron themselves
Accessibility	<ul style="list-style-type: none"> • Many patients do not have easy access to medical care • Difficult to get patient to travel to see physician or get medication to patient • Large hospitals have good facilities but many deprived areas have poor facilities

i.v. = intravenous; HIV = human immunodeficiency virus.

i.v. iron sucrose administration were demonstrated while iron not utilized by the hematopoietic tissues helped replenish maternal iron stores [17]. More recent studies have demonstrated i.v. iron to be more efficient than oral iron at increasing Hb levels and replenishing iron stores [1, 4, 6]. The recently published recommendations for the treatment of IDA in pregnancy include i.v. iron as an effective alternative to oral iron during the second and third trimester for pregnant women who fail to respond to oral iron therapy [10] (Table 3).

I.v. iron preparations include iron sucrose, sodium ferric gluconate, low molecular weight iron dextran and newer “next generation” preparations, such as ferric carboxymaltose [10]; however, these preparations have substantially different safety profiles [2]. For example, dextran-containing i.v. iron preparations have been shown to be associated with an increased risk of anaphylactic reactions [2], whilst iron sucrose and sodium ferric gluconate are associated with fewer side effects [2]. Furthermore, subtle structural variations between the iron sucrose formulations produced by different manufacturers may affect the stability of the iron complex and, in turn, the safety and efficacy profile [26].

Additionally, numerous studies have demonstrated the efficacy and safety of i.v. iron sucrose in pregnant (second and third trimester) [1, 12] and postpartum women [6, 10]. Experience with i.v. iron sucrose in the Asia-Pacific region is growing [16, 24, 27] and data are comparable to results from European studies [6, 12], demonstrating that i.v. iron sucrose is effective, provides rapid correction of anemia and is well tolerated in treating IDA during pregnancy [16, 24, 27].

Packed cells or red blood cell transfusion

Although blood transfusions are an effective treatment for IDA, since they deliver exactly what the body needs (red

blood cells) without any further physiological effort, they do not correct the underlying cause of anemia. Furthermore, there are many inherent risks involved with this treatment, including serious infection, incorrect transfusion, negative impact on the immune system and transfusion reactions [7, 13]. Additionally, certain groups of the population may refuse blood transfusions due to religious beliefs, and limited blood supply often means that stock is reserved for emergencies. Therefore, the administration of a blood transfusion should be considered as a last resort when a patient is unresponsive to i.v. iron supplementation or is in a critical condition.

Managing IDA in pregnant and postpartum women in the Asia-Pacific region – present situation

The prevalence of anemia during pregnancy and the postpartum period is a particular problem in the Asia-Pacific region where it is the highest worldwide. In Southeast Asia and the Western Pacific, 48.2% and 30.7% of pregnant women have anemia, but some data indicate that prevalence could be as high as 85.6% and 90.2%, respectively [29] (Table 4). In this region, oral iron and blood transfusions are currently the most common therapies for the treatment of IDA (Table 5). However, these strategies are suboptimal since oral iron is slow to increase Hb to desired levels in moderate-to-severe anemia. Moreover, a limited availability of blood donors, high costs and risk of infection means that blood transfusions should only be used sparingly in very serious cases [7, 13]. It is, therefore, vital that effective guidelines for the treatment of IDA in pregnancy are developed for the Asia-Pacific

region to ensure prompt intervention and optimal care of the mother and developing fetus.

Physicians throughout the Asia-Pacific region face a range of unique challenges when managing IDA in pregnant and postpartum women (Table 6). In some areas, testing for and treatment of anemia during pregnancy are not a priority since there is an acceptance that anemia is commonplace in the general population accompanied by a lack of perception of the consequences of maternal IDA. Also, the high prevalence of thalassemia and malaria in some regions complicates diagnosis and treatment; therefore, identifying the cause of anemia is essential before intervention is initiated. Access to the appropriate therapy is often an issue with geographic and economic barriers, preventing optimal care of patients in greatest need.

Evidence of the efficacy and safety of i.v. iron as a treatment for IDA is growing through a number of international trials [1, 4, 6, 10, 12, 15, 16]. These studies have shown a rapid correction of anemia and a reduced risk of blood transfusions in the peripartum and postpartum period. As a result, the use of i.v. iron as a treatment for IDA has increased in Europe in the obstetric/gynecologic setting. Similar studies

at the local level in the Asia-Pacific region have been lacking and consequently the use of i.v. iron in this region has been limited. Other issues including fear of adverse events, availability of resources and economic viability (Table 6) also restrict the use of i.v. iron in these communities. However, intervention with i.v. iron is expected to grow in the Asia-Pacific region in parallel with evidence from recent trials conducted in this section of the population [16, 24, 27].

Recommendations for diagnosis and treatment of IDA in pregnancy in the Asia-Pacific region

Accepted guidelines to assist physicians treating pregnant women with IDA are lacking in the Asia-Pacific region. An expert panel (Appendix), of physicians involved in the treatment of anemia in the obstetrics/gynecology setting and with long-term experience of iron therapy, was convened to develop a concise and informative set of recommendations for the treatment of IDA in pregnant and postpartum women in the Asia-Pacific region. This manuscript provides these recommendations and aims to raise awareness of the safety and

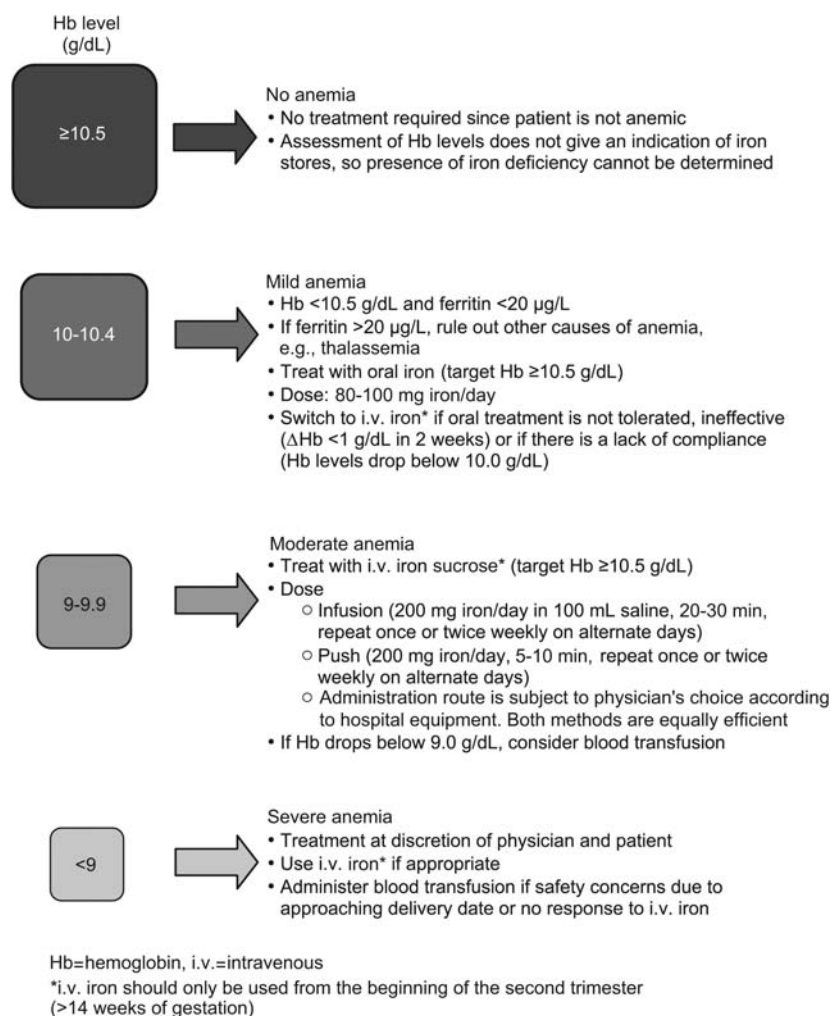


Figure 1 Consensus recommendations for the treatment of IDA during pregnancy in the Asia-Pacific region. IDA = iron-deficiency anemia.

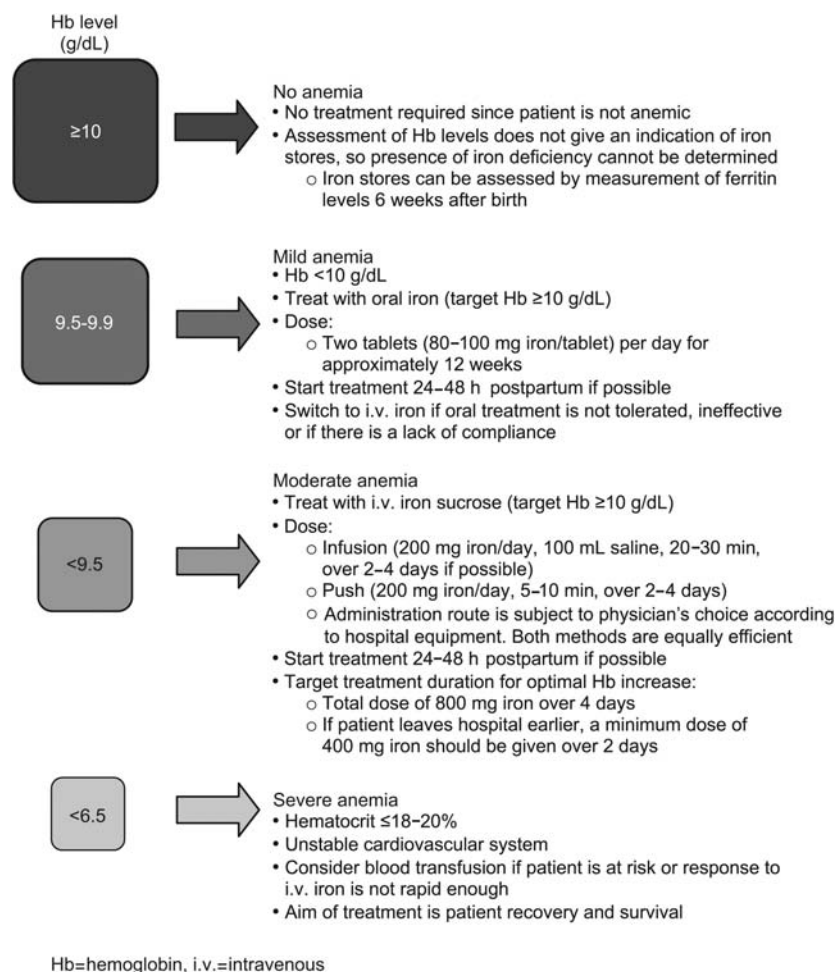


Figure 2 Consensus recommendations for the treatment of IDA during the postpartum period in the Asia-Pacific region. IDA=iron-deficiency anemia.

efficacy of treatments available for IDA to meet the requirements of pregnant and postpartum women in the Asia-Pacific region.

Diagnosis of IDA during pregnancy in the Asia-Pacific region

Anemia in pregnancy is defined by the Center for Disease Control and Prevention as an Hb level of below 11 g/dL in the first and third trimester and an Hb below 10.5 g/dL in the second trimester [23]; likewise, the WHO define anemia in pregnancy as an Hb level below or equal to 11 g/dL [29]. The Hb cut-off levels currently used in practice are often lower than these levels (Table 5); hence, it is important to raise awareness of the criteria used for the diagnosis of anemia in pregnant women. A hematologic profile, including Hb levels and hematocrit, enables the diagnosis of anemia [8] and biochemical markers of iron levels are important for determining the cause of anemia before treatment is initiated. To identify IDA, both Hb (an indicator of anemia) and serum ferritin (an indicator of iron storage) should be assessed: low ferritin levels indicate iron deficiency, while normal-to-high ferritin levels can indicate thalassemia, lead poisoning and

inflammation [25]. Therefore, the appropriate use of markers for iron levels should be established to aid the diagnosis of IDA during pregnancy and the postpartum period.

Consensus recommendations for diagnosis of IDA during pregnancy in the Asia-Pacific region

- Hb <10.5 g/dL
- Ferritin <20 µg/L
- If ferritin >20 µg/L, other causes of anemia such as thalassemia and vitamin B₁₂ deficiency should be excluded
 - Consider C-reactive protein assessment to rule out underlying infection (causes elevated ferritin levels)

Consensus recommendations for diagnosis of IDA during the postpartum period in the Asia-Pacific region

- Hb <10 g/dL
- Ferritin measurement is not recommended in the early postpartum period since it can be normal or elevated due to inflammation
- Treatment can commence once:
 - The cardiovascular system is stable
 - There is no ongoing bleeding

Treatment of IDA in pregnancy and the postpartum period in the Asia-Pacific region

Due to the serious consequences of IDA in pregnancy, prompt and effective intervention is required (Tables 2 and 3). It is important to note that i.v. iron and oral iron are only licensed for the treatment of iron deficiency. Furthermore, the use of i.v. iron is contraindicated during the first trimester of pregnancy. However, the use of i.v. iron is considered safe in the second and third trimester [20]. It is, therefore, advisable to check the labels for both oral and i.v. iron compounds prior to their administration. The consensus recommendations (Figures 1 and 2) target the application of oral iron, i.v. iron and blood transfusion to specific severities of IDA (stratified by Hb level) to ensure the safest and most efficient treatment possible. The Hb cut-off values were agreed by the expert panel to indicate the need for treatment of IDA during pregnancy (Figure 1) and the postpartum period (Figure 2).

Areas requiring further consideration

Recent studies have demonstrated the efficacy and safety of i.v. iron in pregnant (second and third trimester) [1, 4, 12] and postpartum women [6, 12]. Experience with i.v. iron in the Asia-Pacific region is growing [16, 24, 27]. However, further studies in this region are warranted to enhance confidence in the use of i.v. iron among prescribing physicians. Measures to raise awareness of the consequences of IDA are also required to ensure the appropriate testing and prompt treatment of anemia during pregnancy and the postpartum period.

Conclusions

IDA is the most frequent form of anemia during pregnancy and can have serious consequences for both the mother and fetus. The majority of women do not have adequate iron stores to meet the dramatic increase in requirements during the second and third trimester of pregnancy. From a worldwide perspective, IDA in pregnancy is highest in the Asia-Pacific region; however, there has been little guidance in this region for the safe and effective treatment of IDA during pregnancy and the postpartum period. Currently, the main interventions in this region are oral iron and blood transfusions. However, i.v. iron is more effective, provides more rapid Hb correction, corrects iron stores and is better tolerated than oral iron in treating IDA during pregnancy [1, 4, 10]. Furthermore, recent studies have demonstrated the efficacy and safety of i.v. iron in the second and third trimester of pregnancy [1, 4, 10] and in postpartum women [6, 10]. The goal of the recommendations presented here is to reduce the morbidity and mortality associated with IDA in pregnant and postpartum women in the Asia-Pacific region. Consensus recommendations include a definition of anemia as an Hb level below 10.5 g/dL in pregnancy and below 10 g/dL in the postpartum period. The panel also advocates the use of i.v. iron in the second and third trimester of pregnancy to

correct anemia and reduce the risk of transfusion in the postpartum period. Further randomized phase III trials with i.v. iron in the Asia-Pacific region are warranted to optimize clinical outcomes for the mother and developing fetus.

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Conflict of interest

CB is a medical external consultant for Vifor Pharma. The remaining authors have no conflicts of interest to declare.

Appendix

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